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Relevance of albuminuria levels lower than CKD guidelines or when albuminuria emerges as an isolated mortality risk factor beyond CKD definition

Relevância dos valores de albuminúria inferiores aos das *Guidelines* para a DRC ou Quando a albuminúria emerge como um fator de risco isolado para a mortalidade para além da definição de doença renal crónica

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In January 2013, the KDIGO published the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) where was stated "*...We recommend that all people with CKD be considered at increased risk for cardiovascular disease ...*" with a (1A) strength of recommendation[1]. The CKD definition it is now based in two main determinants: a low estimated glomerular filtration rate (eGFR) and the level of albuminuria measured as albumin to creatinine ratio (ACR) in an untimed (spot) urine sample. Each of these determinants can be found together or isolated for the CKD definition[2-4].

The prevalence of eGFR ≤ 60 ml/min/1.73m2 in the general population is ten times that of the patients on dialysis or transplanted[5]. The reason for this difference is mainly due to death of the patients before arriving to the late stages of CKD[6]. This absolute mortality risk is independent of the nature of the cause of the renal disease. This observation links, somehow, the CKD "environment" to the mortality risk. This risk for cardiovascular disease (CVD) and death was definitely established in the meta-analysis by the CKD Prognosis Consortium that demonstrated a strong association of eGFR ≤ 60 ml/min/1.73m^2 with subsequent risk of cardiovascular and all-cause mortality in the general population and in populations with previous increased risk for CVD[2-4]. While for the eGFR the threshold level below 60 ml/min/1.73m2 is for a long time assumed as a clear mortality risk factor, the threshold for albumin is far from being clear. In several clinical settings as in diabetes or hypertension the decrease of eGFR is frequently preceded by the appearance of albuminuria and, on the other hand, not infrequently the decline in eGFR is not followed by albuminuria. This observation gives an independent weight to both variables either as risk factor for CV and all-cause mortality[7].

For the definition of CKD, the KDIGO team chose a threshold for urinary albumin equivalent to an ACR in a random untimed urine sample of ≥ 30 mg/g or

≥ 3 mg/mmol. The rationale for this threshold seems weak once it is mainly based in the observation that that value "... is greater than 3 times the normal value in young adult men and women of approximately 10 mg/g or 1 mg/mmol)...". If it is assumed that the normal value is < 10 mg/g, I think it is arbitrary to multiply by 3 the normal range in the definition of CKD.

It can be understood that, for the case of the CKD definition, an ACR value of 30 mg/g can be accepted, since a lower value would cause an even greater and alarming prevalence of CKD. But for the relevance of albuminuria as a mortality risk factor, beyond CKD definition, the threshold must be lower[8].

Once again, the meta-analysis by the CKD Prognosis Consortium[3] showed a sustained and continuous increase in CV and all cause mortality for ACR levels as low as 5 mg/g. This observation clearly points to ACR as a sensitive marker of mortality risk assessment at values far below the common alerts that we have been taught.

WHAT IS THE LINK BETWEEN ALL BODY TISSUES?

Since the early 1980's, the endothelial cells (EC) lining the vascular tree have gained a paramount importance in the understanding of the homeostatic language between the intra and extra-vascular territories and between local and systemic interactions. An enormous amount of EC functions emerged from animal and clinical investigation[9]. Vascular endothelial cells line the entire circulatory system, from the heart to the smallest capillaries. The recent knowledge that the endocardium and systemic ECs share the same embryogenic lineage permits the conceptual linkage between cardiac and systemic endothelial function and dysfunction[10]. Among these functions are fluid and solute filtration, blood vessel tone and blood flow regulation, haemostasis with anti-thrombotic activity, anti-adhesion and neutrophil recruitment, and hormone trafficking regulation.

The vital role of the endothelium is achieved through the presence of membrane-bound receptors for numerous proteins, lipid-transporting particles, metabolites, and hormones, as well as through specific junctional proteins and receptors that govern cell-cell and cell-matrix interactions. Intra-vascular perturbations that disrupt ECs quiescence that may occur at sites of inflammation or high hydrodynamic shear stress induce a prothrombotic and antifibrinolytic microenvironment[9]. The endothelium, as a whole, can be viewed as an organ, with a 350 m2 surface area and only a small mass of 110 g[11]. The surface of the ECs distribution throughout the vascular bed accompanies the distribution of all the vessel types, with a 3000:1 proportion from the capillaries and postcapillary venules to the larger arteries[12]. These territories (the so-called exchange segment of the vascular tree), control the exchange of molecules between the blood plasma and the interstitial fluid, while maintaining blood and tissue homeostasis. All capillaries are lined with endothelial cells supported by a basement membrane. However, they differ in the details of this basic structure, as well as in the type of supporting cell they possess. The consequent multilayer arrangement of capillary walls ensures that they create a multicomponent and composite exchange barrier[13].

WHICH COMPONENT OF THE ENDOTHELIAL CELL IS THE VASCULAR GATEKEEPER?

In 1966, with the development of ruthenium red, a cationic reagent for electron microscopy, it was for the first time detected a fine cover of the endocapillary layer[14,15]. This EC surface cover was named glycocalyx (sweet coat), mainly composed of proteoglycans and glycoproteins. However, until recently, relatively little attention was paid to this endothelial glycocalyx layer (EGL)(16). Searching, since 1990, by decade in the PubMed for endothelium and glicocalyx, the average number of publications was between 31000 and 48000 for the former and between 480 and 510 for the latter.

The EGL is composed mainly of glycoproteins, sulphated proteoglycans, hyaluronic acid, sialic acids, and plasma proteins. Heparan sulphate is the most abundant proteoglycan in the EGL (± 50–90%) and generally co-expresses with the second most abundant proteoglycan, chondroitin sulphate, in a 4:1 ratio. Additional studies indicate that the transmembrane protein syndecan-4, a member of the heparane

sulphate family of proteoglycans, is linked to the actin cytoskeleton through actin-binding proteins providing the direct association between the EGL and the underlying cytoskeleton for mechanotransduction[17,18]. The EGL is a strong anionic mesh anchored to the EC surface were multiple soluble molecules are impregnated like superoxide dismutase or antithrombin III. This gel type lining is a dynamic interface between blood and EC. The EGL covers all EC along the vascular bed and its thickness and integrity are of major importance for the contact of the blood components and the EC surface receptors and adhesion molecules. The thickness is higher in large vessels than in capillaries. The EGL is a very fragile structure permanently shedding and regenerating easily affected by enzymatic or mechanical shear stress[18]. The EGL integrity is of pivotal importance in promoting leukocyte rolling and reducing adhesion, in preventing albumin leak and keeping the capillary permeability, in maintaining local antithrombotic homeostasis, in maintaining capillary integrity against oxidative stress. It is now clear that the EGL is determinant as a gatekeeper of the vascular tree and especially at the level of the microcirculation.

ALBUMINURIA AS THE MARKER OF GLYCOCALYX INTEGRITY

At the microcirculation, capillaries and postcapillary venules, the endothelium may be described as continuous, fenestrated or discontinuous. In continuous endothelia, one cell directly contacts the next at intercellular junctions. Endothelia may also possess fenestrations, with transcellular cytoplasmic holes, which may or may not contain diaphragms. The mature glomerular endothelium is characterized by fenestrations without diaphragms but covered by glycocalyx[19,20]. In discontinuous endothelium there are significant gaps between adjacent cells where basement membrane may also be absent. For several years, the importance of glomerular glycocalyx was evident[21]. But, until recently, papers concerning proteinuria mechanisms and albuminuria did not address the importance of the glycocalyx as the fist and eventually most important anionic barrier for the glomerular leak of albumin[22,23].

With this knowledge, it is intuitive to admit that the loss or malfunction of the glycocalyx delicate structure can follow the "small" amounts of albuminuria now known to be associated with endothelial disease. While the higher amounts of albuminuria can easily be associated with the classical glomerular pathology, the lesion of the glomerular glycocalyx, as part of the systemic endothelial glycocalyx layer (EGL) lesion, is far more difficult to prove and study.

Recently new insights arrive from clinical and experimental investigation associating glycocalyx lesion to some systemic disease states like diabetes I and II[24,25], capillary leak in sepsis[26,27], ischaemia and reperfusion[28,29], atherosclerosis[30,31] and CKD[32].

Vascular oxidative stress is an important factor leading to endothelial dysfunction and has been identified as a significant contributor to the progression of atherosclerosis and other vascular complications of diabetes and CKD. Excessive generation of reactive oxidative species (ROS) ROS disrupt EGL barrier properties[33].

One of the known causes of vascular stress is water and sodium overload. It was demonstrated that sodium overload transforms the endothelial cells from a sodium release into a sodium absorbing state by disrupting glycocalyx integrity. The specific aldosterone antagonist, spironolactone, prevented these changes. These observations led to the conclusion that the endothelial glycocalyx serves as an effective buffer barrier for sodium and damaged EGL facilitates sodium entry into the endothelial cells. This could explain endothelial dysfunction and arterial hypertension observed in sodium abuse[34] and the benefit of aldosterone antagonists in cardiovascular risk reduction. In recent years a great deal of attention has been directed to the endothelial glycocalyx layer and most of the new knowledge reinforces the main importance of this fragile structure in keeping microvascular and organ integrity.

Low levels of albuminuria can represent, in a near future, a simple and sensitive method for monitoring EGL *in vivo* and, probably, when used as a time sequential variable, also an important and clinically relevant data to monitor and evaluate individual cardiovascular risk.

Conflict of interst statement: *None declared*

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